divisional application. Accordingly, Claims 1-5, 35 and 36 are now under consideration. Favorable reconsideration and allowance of the application is respectfully requested.

The Specification has been amended to correct inadvertent typographical errors and to include the ATCC accession number, for the deposit made before filing but which received its designated accession number after filing. No new matter has been introduced.

Claims 1-5 have been rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking an adequate written description for the cell lines of the invention to evidence that Applicants are in possession of the claimed invention (Office Action at Page 2, fourth paragraph). In particular, the Examiner has interpreted the claims as drawn to cell lines with desired functional properties rather than an actual description of the cell lines themselves. Applicants submit that the cells lines are properly and sufficiently described. In the first instance, the claims recite a cell line composed of cells which are immortalized mammalian cells. This characteristic is not a mere desired functional property but rather describes the state of the cells (immortal versus non-immortal or primary cells) and their source. Second, the term *Stat1*$^{-/-}$ is a shorthand scientific representation, akin to a chemical name, which is well accepted in the art for denoting the genotype of the cells, i.e. the actual makeup of the cells' genome, and in this case indicates that the genome of the cells is homozygous for a null allele of a *Stat1* gene. Again, this characteristic is not a mere desired functional property but rather a description of the actual physical state of the genome of the cells with respect to *Stat1* as being null alleles. While Applicants firmly believe that use of the term *Stat1*$^{-/-}$ is clear and evidences their possession of the invention, especially when read in conjunction with the definitions of that term in the Specification (e.g., at Page 2, Line 25 and at Page 8, Lines 17-19) and

the data provided in the Examples, in the interest of expediting prosecution, Applicants have amended Claim 1 to expressly recite that the cell line is "homozygous for a *Stat1* null allele." Support for this amendment is found in the above cited definition passages. Moreover, the Specification fully describes how to make and use the claimed cell lines without resort to undue experimentation and any remaining aspects of this written description rejection as they relate to enablement are fully discussed below in response to the Examiner's objection to the specification for lack of enablement.

Accordingly, Applicants believe that the present claims satisfy the written description requirement and respectfully request withdrawal of this rejection.

The Examiner has objected to the Specification under 35 U.S.C. §112, first paragraph, as allegedly being a non-enabling disclosure and has suggested depositing the cell lines of the invention in accordance with the conventions of the Budapest Treaty. While Applicants deposited a representative cell line under the terms of the Budapest Treaty before the effective filing date of this application, Applicants believe that the Specification teaches the ordinarily skilled artisan how to obtain cell lines of the invention by a repeatable method with a reasonable expectation of success and that a deposit of each and every cell line is not necessary to satisfy the requirements of 35 U.S.C. § 112, first paragraph. In other words, and as fully explained below, the Specification provides sufficient guidance and teaching that one of ordinary skill in the art is more likely going to obtain a cell line of the invention by following the teaching of the Specification.

Techniques needed to create cell lines having a specific genotype are well known. *See, e.g.,* Joyner (1993) Gene Targeting, A Practical Approach, Oxford University Press, Oxford, which was also cited in the Specification at Page 6, Linew 24-25. Methods

specifically applicable for production of *Stat*$^{-/-}$ cell lines are described in the Durbin and Brown references cited in the Specification at Page 2, Line 22 and at Page 9, Line 36 to Page 10, Line 1, respectively. Moreover, the Detailed Description of the Invention discusses how the techniques of the Durbin and Brown references are used to specifically create cultured cell lines that are homozygous for null alleles of Stat1 (Page 9, Line 30 to Page 10, Line 21) followed by immortalization if necessary. Finally, Examples 1-3 actually demonstrate that *Stat*$^{-/-}$ cell lines are obtainable by straightforward techniques and respectfully draw the Examiner's attention to Example 1 (Page 19) which describes four different *Stat*$^{-/-}$ strains from which at least three independent cell lines are established.

The Examiner's suggestion that this invention requires isolating a single cell line and testing it to see whether it has the desired biological activity miscomprehends how the cell lines of the invention are made. First, the cell lines are not simply "isolated" for testing, rather one chooses, for example, to test the cell lines obtained after being subject to the selective pressure for a particular trait (typically development of antibiotic resistance) that accompanies deliberate, recombinant targeting of the genomic *Stat1* gene with a vector having a known or genetically-engineered *Stat1* null allele coupled to the trait being selected, and the repeat of similar targeting, to produce to a cell line that is homozygous at the *Stat1* gene. In this method, a negative selection process eliminates cells that do not carry the desired traits and greatly enriches for those that do.

Applicants respectfully point out that while selection and establishment of the immortalized *Stat1*$^{-/-}$ cell lines of the present invention can involve two rounds of targeting and repeated subculturing to immortalize the cells, it is not a "make and test" scenario which lacks a reasonable expectation of success. Indeed, one of ordinary skill in

the art recognizes that the steps in constructing immortalized *Stat1*$^{-/-}$ cell lines involves biological processes wherein cellular genotype is deliberately and directly altered followed by adaption of the cells for indefinite growth under defined culture conditions (or vice versa). The fact that it may take several rounds of subculturing or that the genetic manipulations may be successful on anywhere from a few percent to 25 or 50 percent of the initial target cell population[1], reflects this adaptive process, and should not be interpreted to mean that the process itself is based on trial and error, is unpredictable or that the subject matter of the claimed invention is obtained by nonrepeatable methods. The Applicants respectfully stress that selection of cells in this manner is not a haphazard, "make and test" gamble, but is instead a well-defined culture and selection method in which undesired cell lines (i.e. those that "do not work") are not selected and those that survive the process may predictably be expected to have the requisite *Stat1*$^{-/-}$ phenotype. Thus, by virtue of the cell lines undergoing the selection process, coupled with the demonstrated success of Applicants, those practicing the invention are more likely than not going to expect to obtain a cell line of the invention.

As these arguments establish the invention is enabled, they likewise establish that a deposit of biological material is unnecessary.

Hence, Applicants respectfully submit that the description of the invention, the examples presented in the Specification and the guidance in the Specification are ample to teach the ordinarily skilled artisan how to make and use the invention without resort to

---

[1]Considering that such experiments are typically done on a minimum of 10^5 cells (and often many more) even a targeting rate of 0.1% means that at least 100 cells are available for expanision, a second round of targeting and immortalization.

undue experimentation. Accordingly, Applicants believe this objection to the Specification should be withdrawn.

In view of the foregoing amendments and remarks it is firmly believed that the subject invention is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Dated: April 21, 1999

M. Lisa Wilson
Reg. No. 34,045

KENYON & KENYON
One Broadway
New York, NY 10004
Tel: (212) 425-7000
Fax: (212) 425-5288

76451